

EXHIBIT A153

World
Cancer
Research
Fund



American
Institute for
Cancer
Research

CUP Continuous
Update
Project

Analysing research on cancer
prevention and survival



Judging the evidence

2018



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WORLD CANCER RESEARCH FUND NETWORK

Our Vision

We want to live in a world where no one develops a preventable cancer.

Our Mission

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

Our Network

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.



Analysing research on cancer prevention and survival



Our Continuous Update Project (CUP)

The Continuous Update Project (CUP) is World Cancer Research Fund Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (see inside back cover).

Through this process the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of World Cancer Research Fund Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. [Judging the evidence](#) is one of many parts that make up the CUP Third Expert Report: for a full list of contents see dietandcancerreport.org

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

How to cite the Third Expert Report

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The whole report: World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org

Key

See **Glossary** for definitions of terms highlighted in *italics*.

References to other parts of the Third Expert Report are highlighted in [purple](#).

1. Introduction

Globally the burden of cancer and other non-communicable diseases is increasing. Diet, nutrition and physical activity play a key role in prevention of these diseases, and evidence-based recommendations are necessary to help people make healthy choices in their daily lives (see [Recommendations and public health and policy implications](#)).

In order to produce recommendations, the causal factors need to be identified; this requires a clear, systematic and rigorous process. The majority of evidence in relation to diet, nutrition and physical activity is based on observational studies and therefore attributing causal risk is challenging. The Bradford Hill criteria can be applied to traditional epidemiological data as a framework for causal inference [1]. The Bradford Hill criteria are the basis for the Continuous Update Project (CUP) systematic review analyses and the criteria for judging the evidence.

The WCRF/AICR Cancer Prevention Recommendations are derived from systematic reviews of epidemiological evidence, supported by experimental evidence from human and animal studies. The aim of this work is to determine which aspects of diet, nutrition and physical activity protect against cancer and which are causes of cancer.

The task of the Panel has been to assess and judge a comprehensive review of a range of evidence to draw conclusions and make recommendations, using a systematic and transparent process.

The methods used by the Panel are based on those used for the 2007 Second Expert Report [2]; there have been some changes to ensure the most appropriate statistical methods are followed and to make the process more efficient. The best evidence that aspects of

diet, nutrition and physical activity can modify the risk of cancer does not come from any one type of scientific investigation. It comes from a combination of epidemiological and other studies, supported by evidence of plausible biological mechanisms. Such comprehensive evidence has been collected in the form of 18 *systematic literature reviews* (see [CUP SLRs](#)), including 17 on cancer prevention and one on breast cancer survivors (see [CUP breast cancer survivors report 2014](#)), specially commissioned as the basis for the CUP (see [CUP cancer reports](#)). In addition, as 12 of the 17 cancers reviewed are linked to greater body fatness, a separate review on the determinants of weight was undertaken (see [Energy balance and body fatness](#)). Owing to the large amount of published evidence, [Energy balance and body fatness](#) was conducted as a review of published reviews, rather than a systematic literature review of individual studies and meta-analyses, as used for the CUP cancer reports. For the CUP cancer reports the epidemiological evidence and expert reviews of currently prevailing primary hypotheses of cancer-specific mechanisms amount to a comprehensive examination of the relevant types of evidence, organised using a common methodology.

The evidence was judged by the CUP Panel of independent experts, with a view to making recommendations. Recommendations were generally based on strong evidence, when the Panel judged that a particular *exposure* was convincingly or probably causally linked to cancer risk. These two key judgements of ‘convincing’ and ‘probable’ denote the Panel’s judgement that the evidence of causality – that a factor either decreases or increases the risk of cancer – is strong enough to justify recommendations (see [Recommendations and public health and policy implications](#)). The judgements of the Panel along with a summary of evidence supporting the Recommendations can be found in the [Exposures sections](#) and [CUP cancer reports](#).

2. Randomised controlled trials

A *randomised controlled trial (RCT)* is an experiment in which participants are randomly assigned to groups, often called intervention and control groups, to receive or not receive an experimental intervention. The main use of RCTs has generally been to test the efficacy of drugs and other medical treatments.

In a 'double-blind' RCT, neither the participants nor the investigators know to which group (intervention or control) the participant has been assigned. Blinding is used because the knowledge of group assignment might influence study results, but it is usually impossible to achieve in trials involving physical activity or those investigating foods and drinks in their usual form.

RCTs may yield powerful evidence of the effect of a specific dietary constituent. The particular constituent selected for study is often derived from epidemiological studies (see **Section 3**) that have shown associations between particular food groups, individual foods or nutrients. However, *exposure* for the duration of a trial cannot reproduce the full exposure over decades (or longer) implied in observational studies, and therefore interpretation of differing results from epidemiological studies and trials is complex. In addition, because dietary constituents are often clustered within foods and patterns of diet are linked to other health-related behaviours (for example, tobacco smoking or physical activity), there is always a possibility that the actual active agent, combination of agents in the foods or other factor has not been tested in the trial. Furthermore, dietary constituents that may be protective as part of an overall diet may have unexpected effects in isolation, especially at doses higher than those found in normal diets. For example, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC Trial) of male

smokers in Finland, high dose beta-carotene supplementation increased the incidence of lung cancer [3].

The RCT is considered the gold standard of clinical trials. However, due to the limitations enumerated here, there are few RCTs investigating the effect of diet, nutrition and physical activity on cancer risk.

3. Epidemiological evidence

Epidemiological research describes and seeks to explain the distribution of health and disease within human populations. This type of investigation is known as observational. By relating differences in circumstances and behaviour to differences in the incidence of disease, associations are identified that may or may not be causal. In epidemiological studies, an '*exposure*' is a factor or condition that may or may not influence the risk of disease. These types of studies are more appropriate for the study of associations between diet, nutrition, physical activity and cancer. In contrast to RCTs, causal associations are not possible; however, causal inferences can be made. This is explained further in **Section 8**. In the Continuous Update Project, diet, nutrition and physical activity are the broad '*exposures*' investigated, though each of these domains comprises a range of more specific factors that are exposures in their own right (for example, diet includes specific foods (such as *processed meat*) and drink (such as alcoholic drinks). The methods summarised here and applied to cancer are also used to study and understand other diseases. There are a number of issues to consider concerning interpretation of the evidence (see **Box 1**).

Box 1: Issues concerning interpretation of epidemiological evidence

Interpretation of epidemiological evidence on diet, nutrition and physical activity and the risk of cancer is complex, and expert judgement is essential. General considerations that need to be taken into account when evidence is assembled and assessed include the following:



Patterns and ranges of intakes: Most epidemiological studies are carried out in *high-income countries*. Their findings may have limited application in countries where dietary and physical activity patterns are different. Indeed, even studies conducted in high-income countries may have limited relevance to the whole population of the country if the ranges for the *exposures* examined are relatively narrow. Some foods that are important dietary constituents outside high-income countries may rarely be examined.



Classification: Following from the above, studies usually classify food and drink consumption and physical activity in ways that correspond to the patterns of *high-income countries*. Their findings may over-emphasise the significance (or insignificance) of foods and drinks commonly consumed in high-income countries, and may overlook foods and drinks consumed in other parts of the world. The same considerations apply to types of physical activity. Issues of the generalisability of research may impede our understanding, not only in middle- and *low-income countries*, but also globally.



Measurement: Many dietary and physical activity exposures are difficult to assess quantitatively and are thus measured imprecisely. It is easier to measure intakes of food than intakes of dietary constituents of foods. This can lead to a lack of importance being attributed to exposures that are not easy to measure.



Terminology: For some exposures, there are no generally agreed definitions. Examples include '*dietary fibre*' and '*processed meat*'. Also, some common definitions may disguise real differences; for example, different types of '*dietary fibre*' have different biological effects.



Cancer outcomes: Cancer registries with data on incidence and mortality are available in many countries and are a useful source for cancer outcomes. However, completeness of data varies by country. Cancer is a complex disease with many possible sub-types for each cancer type; for example, stomach cancer includes cardia and non-cardia sub-types. Diet, nutrition or physical activity may affect the risk of specific cancer sub-types differently. Where risk relates to certain sub-types only, this relationship may be lost when analyses are conducted across all types of that cancer.



Study design: Each study design has its advantages and limitations. The hierarchy of epidemiological evidence places *cohort studies* above *case-control studies*, with *ecological studies* and case reports at the bottom. There are merits in considering a number of different study designs. Cohort studies are likely to be the main source of evidence owing to the long latent period for cancer to develop and also to their prospective design. However, in some circumstances case-control studies and ecological studies may also make a useful contribution to the evidence (see **Section 7**).



Shape of the association: The association between exposures and cancer may be linear, showing either increasing or decreasing risk with higher levels of exposure (see **Boxes 2 and 3**). It is important to also consider other shapes of an association as these may be significant for the development of recommendations. There may be a threshold above which an association is found or a plateau where no further increase or decrease in risk is observed. There may also be a number of different curves in which the direction of association may differ depending on the level of exposure; for example, J- or U-shaped curves (see **Box 4**).



Confounding: A confounder is a factor associated with both the outcome (that is, cancer) and the exposure being studied but is not a result of the exposure. It is never possible with observational studies to eliminate completely the possibility that an evident result of an exposure is caused at least in part by another factor. Examples of common confounders are *socioeconomic status* and tobacco smoking.



Effect modification: *Effect modification* (or effect-measure modification) occurs when a measure of effect for an exposure changes over levels of another variable (the modifier) [4]. Effect modifiers can sometimes even change the direction of an effect. One example is menopausal status and body fatness and breast cancer. In premenopausal women greater body fatness is associated with a decreased risk of breast cancer; however, in postmenopausal women it is associated with an increased risk of breast cancer.



Reporting bias: Studies that rely on self-reporting of dietary intake are prone to systematic bias. People tend to over-report consumption of foods and drinks they believe to be healthy, as well as being physically active, and under-report foods and drinks they believe to be unhealthy. The impact of this bias is likely to be greater for retrospective rather than prospective assessment of diet; this is a particular issue for case-control studies. Under-reporting of energy intake has been shown to be associated with factors such as age, overweight and obesity, perceived body size and other personal characteristics [5–12]. In prospective studies the impact of reporting bias is likely to lead to random misclassification of dietary intakes and thus make it more difficult to detect real associations. It is widely acknowledged that food frequency questionnaires (FFQs) do not provide reliable estimates of absolute energy intake but provide better estimates for energy as a percentage of fat, protein, etc. They are primarily used to rank participants of studies by level of intake and not to assess precise intake.



Production, preservation, processing, preparation: Studies of foods and drinks, and of food groups, may neglect the effects of methods of production, preservation, processing and preparation (including cooking). They also tend to underestimate the significance of foods and drinks combined in dishes or meals, and as components of whole dietary patterns.

3.1 Cohort studies

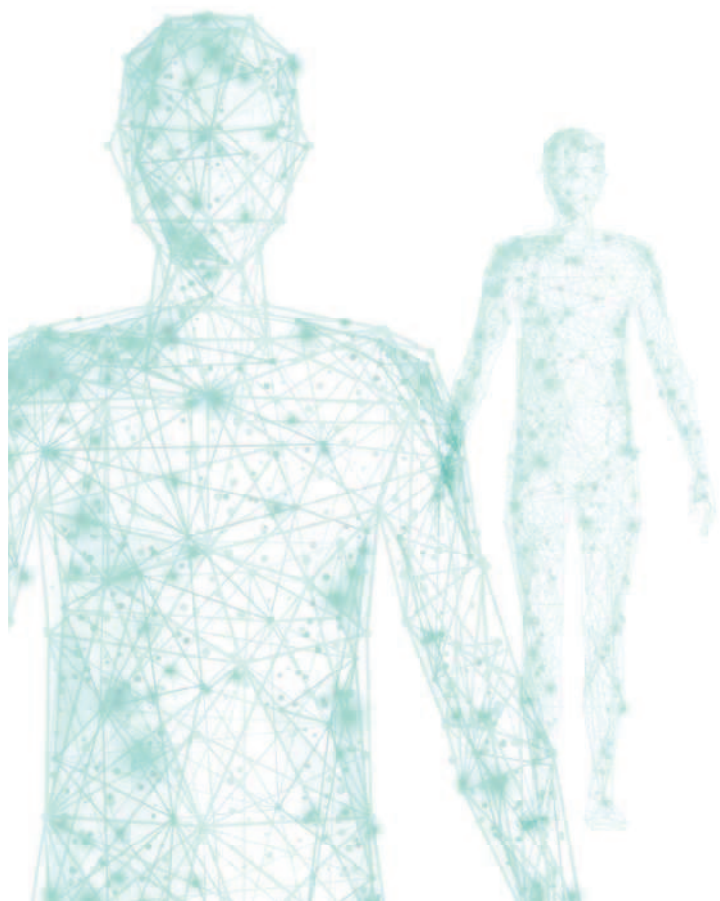
In prospective *cohort studies* (usually called simply cohort studies), the diets, body fatness (for example, *body mass index* or BMI) and/or physical activity levels of a large group (cohort) of people who are assumed to be healthy are assessed, and the group is followed over a period of time. During the follow-up period, some members of the cohort develop and are diagnosed with cancer while others do not, and comparisons are then made between these two groups. Because measurements are made before any cancer diagnosis, cohort studies are not subject to recall bias. A single cohort study allows examination of the associations between diet and physical activity and multiple types of cancer and other diseases. Also, in cohort studies, blood and tissue samples are often collected and stored for future analysis. Finally, cohort studies provide the opportunity to obtain repeated assessments of participants' diets at regular intervals, which may improve the dietary assessment and help to capture changes in *exposures* over time (such as weight gain, dietary changes).

Cohort studies may need to be very large (up to tens or even hundreds of thousands of participants) to have sufficient *statistical power* to identify factors that may increase cancer risk by as little as 20 or 30 per cent. They are better suited to common rather than rare cancers. Sufficient variation in exposure to each factor, within the cohort, is required in order to detect associations between the factor and cancer. There is also the opportunity to assess dietary and other habits repeatedly over the follow-up period. If baseline diet is recorded and there is no repeat measurement of diet, participants may change their habits during the course of follow-up and this may affect their risk of cancer.

Cohort studies are susceptible to *bias* through confounding (where the association is at least in part due to another factor), so it is necessary to ensure that all potential *confounders* are measured. Statistical analyses can be conducted to adjust for confounding; however, there is always the possibility of residual confounding (for more information on confounders, see **Box 1**).

Generalisability of population-based cohort studies could be an issue if response or follow-up rates are poor and those who take part and are followed up differ in some way from those who do not. For example, it could be that the healthiest people agreed to take part.

Cohort studies are expensive, so they have been conducted mostly in *high-income countries*, although increasing numbers of cohort studies are now being conducted in middle- and *low-income countries*. Cohort studies can be made more cost effective if they study many cancers.



3.2 Case-control studies

In *case-control studies*, people diagnosed with a specific type of cancer ('cases') are compared with otherwise similar people who have not been diagnosed with cancer ('controls'). The control group is a sample of the population from which the cases arose and provides an estimate of how the *exposures* being studied are distributed in that population.

Identifying and enrolling appropriate controls is a major challenge in case-control studies [13–15]. Case-control studies are subject to recall bias, which can occur when participants recall past dietary intake or physical activity. It is differentially affected by whether they are cases or controls in the study. Low response rates or participation in research studies is an increasing problem in *high-income countries*. Participants may have different behaviours to non-participants, and such differences may vary between cases and controls. However, case-control studies can be completed over shorter periods of time and are usually less expensive than *cohort studies* (see **Section 3.1**). Case-control studies, like cohort studies, are susceptible to *bias* through confounding.

A '*nested*' case-control study is carried out within an existing cohort study. In this type of study, all of the cases in the cohort are compared with a sample of the participants who have not developed cancer (controls). A nested case-control study has the strengths of a cohort study – notably that diet is assessed among study participants prior to the diagnosis of cancer, thus avoiding recall bias – but is less expensive to conduct, as only a sample of the non-cases is included in the analysis. It is typically done for stored biospecimens involving expensive bioassays.

3.3 Other study designs

3.3.1 Descriptive studies

The most fundamental information about cancer comes from statistics on cancer incidence and mortality. The International Agency for Research on Cancer, a branch of the World Health Organization, compiles international cancer statistics using data from national and regional cancer registries around the world [16].

Descriptive epidemiology informs cancer surveillance programmes and is an essential tool for determining patterns of cancer, relative rates of cancer and other diseases, and changes in patterns and trends over time.

3.3.2 Migrant studies

Migrant studies compare cancer rates for migrants and for their offspring in their current country of residence with rates in their country of origin. These studies show that populations migrating between areas with different rates of cancer incidence acquire the rates characteristic of their new location for some cancers, often after only one or two generations [17]. This shift shows that environmental, rather than inherited, factors are primarily responsible for the large differences in cancer rates in different regions and countries. Although it is not clear what exact factors contribute to cancer risk, these types of studies have been hugely informative in the development of observational studies.

3.3.3 Ecological studies

Ecological studies are designed to explore relationships between environmental factors and disease among populations rather than people. Although ecological studies, like other observational studies, may suggest a relationship between a specific environmental factor (such as an aspect of diet and nutrition) and a disease, the actual causal relationship

may be with a different 'confounding' factor (such as tobacco smoking), which may or may not be associated with the environmental factor being investigated. Ecological studies have the advantage of being able to compare the very wide ranges of *exposure* that occur worldwide. However, it is difficult to identify potentially causal factors.

Ecological studies such as those using food balance sheets [18] that provide dietary information on populations, and although unable to control for *confounders*, are often used to identify associations or trends and hypotheses that can be tested in more rigorous study designs.

4. Meta-analysis

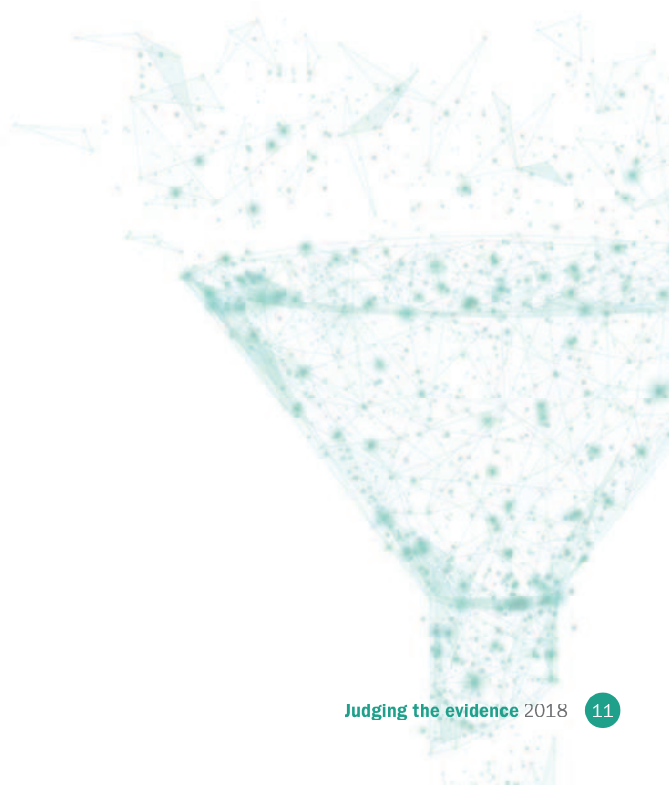
Owing to the interest in the study of diet, nutrition, physical activity and cancer a large number of studies – particularly *cohort and case-control studies* – have been published, and this has allowed systematic reviews and meta-analyses to be carried out. The growth in the number of cohort studies and the improvement in the quality of these studies have provided greater confidence in the accumulated evidence.

Meta-analysis is a method used to combine the results of several studies that address similar questions. It is used to combine observational studies or RCTs, to give greater *statistical power* to detect important associations. Unless an epidemiological study is sufficiently large, modest but potentially important associations can be missed.

Study-level meta-analysis provides single estimates of association or effect using information from multiple studies, ideally of similar design. The greater statistical power allows the detection of less obvious associations, as well as the examination of possible *dose-response* relationships

(see Box 2). Meta-analysis is often displayed graphically (see Box 3). Ideally the studies should all provide a similar result if they address the same question. It is important to identify whether the variation in results between studies is greater than that expected by chance (*heterogeneity*). This heterogeneity can be statistically quantified using a measure called I^2 , which ranges from 0 to 100 per cent and describes the proportion of total variation in study estimates that is due to heterogeneity [19]. If there is high heterogeneity, in particular in the direction of the association or effect, this leads to less confidence in the summary result. The CUP Panel regards heterogeneity as low when it accounts for less than 30 per cent of the variability in point estimates and high when it accounts for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size of the effect and the direction of association.

Pooled analysis is a type of meta-analysis in which original individual-level data from various published epidemiological studies of a similar type – usually prospective cohort studies – are combined and re-analysed. The combination of data from multiple studies creates a larger data set and increased statistical power.



Box 2: Dose-response

'Dose-response' is a term derived from pharmacology, where it denotes a change in the effect of a drug according to the dose used. This concept can be applied to any *exposure*, including diet, nutrition and physical activity. For example, different amounts of a food or drink consumed may lead to a different likelihood of any particular outcome, such as cancer. Such a graded response, or biological gradient, may show that higher exposure leads to increased risk, or to reduced risk, and vice versa.

In cohort studies dose-responses take different forms. The relationship may be linear, shown in graphic form as a straight line. There may be a 'threshold' below which there is no significant association, but above which there is an association. This is shown as a horizontal line that inclines or declines once the threshold is reached. Or the association may be to influence risk one way at both low and high levels of exposure, but the other way at intermediate levels of exposure, shown as J- or U-shaped curves. In such cases, the exposure is evidently beneficial or harmful only within certain ranges.

Both dose-response (see **Box 3**) and non-linear dose-response (see **Box 4**) plots are means of displaying graded responses. They show the direction and shape of the association, and allow estimates to be made according to levels of exposure that may influence risk. The demonstration of a biological gradient adds weight to evidence that an exposure may be causal. Diet and physical activity exposures are continuous variables but are often reported in discrete categories. Although this is done for statistical reasons and can make associations easier to detect, the number and location of category boundaries may obscure the true relationship between exposure and the outcome, and non-linear associations may be missed if insufficient categories are used.

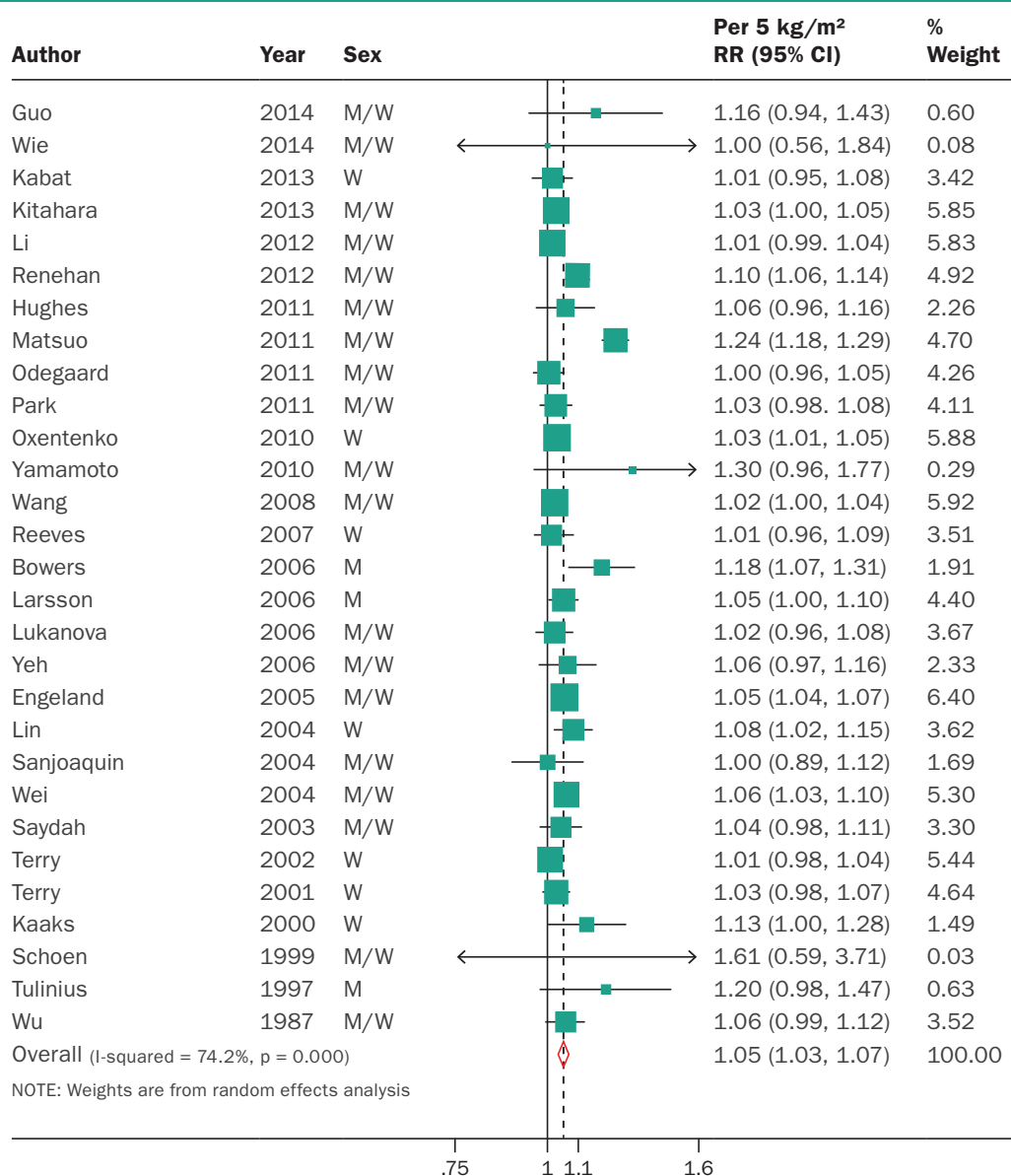
Evidence of dose-response is important when framing recommendations. For example, if the evidence for alcoholic drinks and cancer showed no threshold – that is, the risk of cancer increased with increasing amount of alcoholic drink consumed – then a recommendation based on the evidence for cancer would be to not consume alcoholic drinks (see **Exposures: Alcoholic drinks**). However, if there is clear evidence of a threshold – that is, there was no increase in risk below a certain level of consumption – then the recommendation would differ accordingly.



Box 3: Linear dose-response meta-analyses

This method of analysis assumes a linear *dose-response* relationship between the *exposure* and outcome. Importantly, this method may be used even when there is evidence that the actual relationship is non-linear. It has the advantage of being statistically robust and allows for comparisons between factors with varying types of relationship. However, it may give an inaccurate *point estimate* of the association, particularly at extremes of exposure. The graphic displayed below is the usual method of presenting the results of meta-analysis of a number of studies. In the example, studies are presented that examine the relationship between BMI and colorectal cancer. This plot shows 29 risk estimates from 38 *cohort studies*. The horizontal axis of the plot shows the *relative risk* (RR) and is bisected by the vertical axis, which represents 'no difference in association of risk' between the exposure categories that are compared (the RR is 1.00). Also see Box 5.

Dose-response meta-analysis of BMI and colorectal cancer per 5 kg/m²



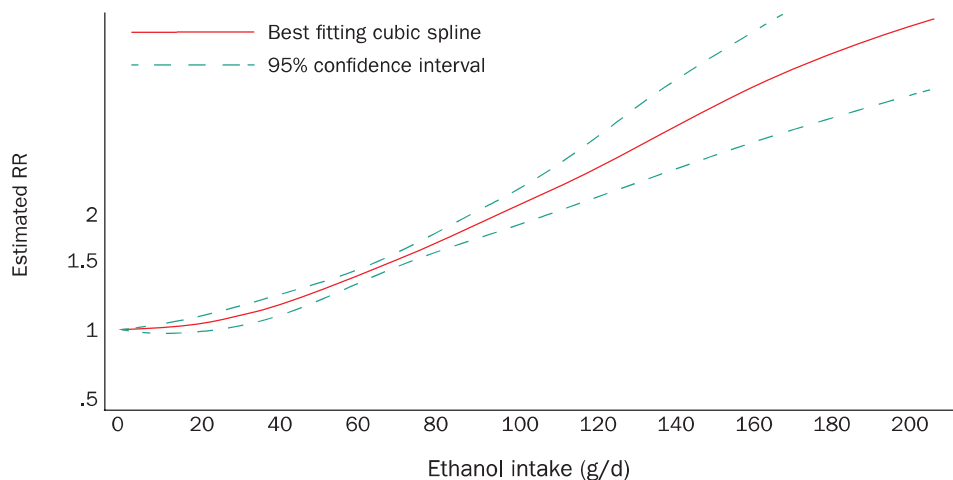
Box 3: Linear dose-response meta-analyses (cont.)

The squares represent the results of each individual study. Each square is centred on the *point estimate* of the RR for that study. The point estimate is the extent to which any exposure (in this case, BMI) is associated with the risk of cancer (in this case, colorectal cancer). The horizontal line running through the squares represents the 95 per cent *confidence interval* (CI) of the estimate. Where no line is apparent, the CI falls within the square. The CI is an indication of how much random error underlies the point estimate; it does not take into account confounding and other forms of systematic *bias* [20]. A CI of 95 per cent indicates a 95 per cent probability that the true population value falls within the CI [21]. The estimate is considered statistically significant when the CI does not cross the vertical axis representing 'no difference'. Looking at the example above, the value of *meta-analysis* is demonstrated: of the 29 risk estimates, 22 are non-significant or only marginally so, of which seven suggest an increased risk (that is, they have an RR of more than 1.00). But taken together, as shown by the summary diamond, an overall significant association is shown, consistent with a judgement that body fatness is a cause of colorectal cancer.

The size of each square on the plot represents each study's calculated weight (influence) on the combined (summary) estimate (the diamond). Calculation of the size of the square takes into account a number of factors, such as the number of people in the study and the event rate (here, the rate of colorectal cancer occurrence). The diamond summarises the meta-analysis. The width of the diamond represents the 95 per cent CI of the overall estimate.

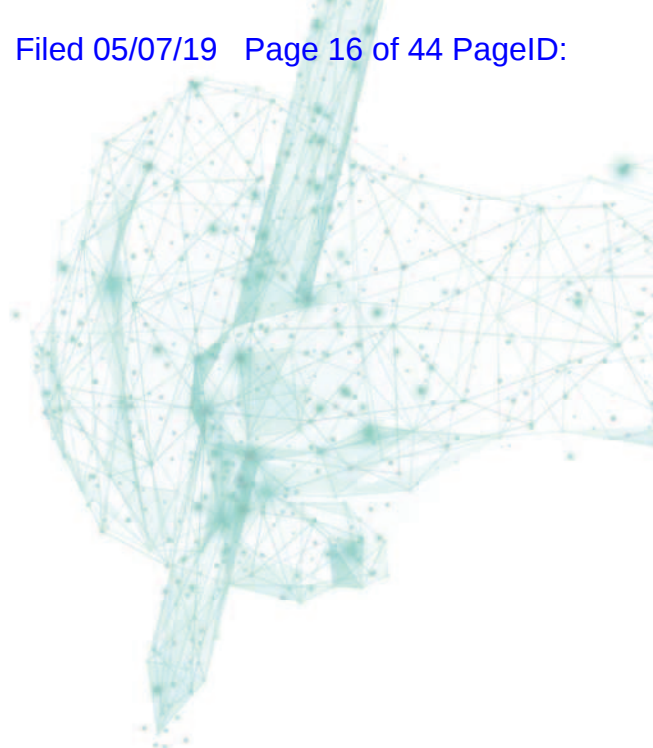
Box 4: Non-linear dose-response analyses

The non-linear *dose-response* method of analysis, as its name suggests, does not assume a linear dose-response relationship between the *exposure* and outcome. It is useful for identifying whether there is a threshold or plateau. In the example below, increased risk of colorectal cancer is observed from an intake of alcohol (as ethanol) of 30 grams per day (equivalent to two drinks). The table provides an assessment of risk at varying levels of alcohol consumption.

Non-linear dose-response associations of alcohol (as ethanol) intake and colorectal cancer

Non-linear dose-response estimates of alcohol (as ethanol) intake and colorectal cancer

ALCOHOL (G/DAY)	RR (95% CI)
0	1.00
10	1.02 (0.98–1.07)
20	1.07 (1.00–1.16)
30	1.15 (1.06–1.26)
40	1.25 (1.14–1.36)
50	1.41 (1.31–1.52)
60	1.60 (1.51–1.69)



Box 5: Quantification of risk

Quantification of the risk of any disease is an essential basis for public health policy planning. It is not enough to know that the risk of cancer is affected by diet. It is also important to know by how much. The strength of a relationship between any risk factor and the occurrence of disease is commonly expressed in terms of *relative risk* (RR). In *cohort studies*, this is the ratio of risk (or *incidence*) of a disease among people with a particular characteristic (say, high consumption of red meat) to that among people without that characteristic (in this example, low or no consumption of red meat).

Relative risks below 1.0 imply a decreased risk, so a relative risk of 0.5 for high compared with low consumption implies a halving of risk. Relative risks above 1.0 indicate an increased risk. The chance of developing cancer over a stated period of time – for example, a lifetime (absolute risk) – is also important. Small RR values, when consistent, are important for indicating the population burden of cancer when the number of people affected is large. A large RR (that is, 2.0 or more) of a rare type of cancer amounts to only a small absolute risk, which may reasonably be considered not significant either by public health planners or by people assessing their own choices. By contrast, a small RR may amount to a large number of cases for a common type of cancer. For example, an increased risk of 10 per cent implied by a RR of 1.10 would amount to many extra cases of colorectal and breast cancer in Europe and North America, where these cancers are common. Assessment of small RRs depends on the size and quality of the studies in which such risks are identified. Small RRs may amount to strong evidence if consistently found in large, well-designed studies.

5. Experimental evidence

Studies such as human intervention studies using biomarkers or investigating mechanisms, and animal and *cell line* experimental studies complement epidemiological and RCT findings and can offer insights into biological plausibility and pathways between *exposure* and disease. As mentioned earlier, epidemiological studies and trials have both strengths and limitations. The primary advantage of experimental studies is the ability to control for factors except the specific parameter of interest, the latter of which is assigned at random. The environment of these research studies is defined by chosen experimental conditions; precise manipulations can be made and relatively exact measures taken. Occasionally the test participants are human volunteers, but usually such studies are conducted in animal models of *carcinogenesis* (in vivo) or using human or animal cells grown in the laboratory (in vitro).

5.1 Human studies

Human intervention studies are usually conducted in free-living situations with varying degrees of control. In some studies, such as the VITamin D and OmegA-3 Trial (VITAL), participants are randomised and blinded to the intervention (for example, vitamin D supplements) [22]. However, blinding is not so easy in food-based intervention studies. In some studies, human volunteers are studied in

a controlled environment, such as within a metabolic unit, where their diets and physical activity levels can be highly regulated and measured. Although the feasible duration of such studies is limited, they represent the most highly controlled approach for human studies as *exposures* can be defined precisely, unlike in studies of free-living subjects.

5.2 Live animal models

Laboratory animals can be used to test the effects of diet, nutrition and physical activity on the development of cancer. Both the *exposures* and the genetic background can be controlled to an extent that is not feasible in humans. Human genes can be added to animals' DNA (creating transgenic animal models) or key genes can be removed (creating 'knockout' animal models) to address specific research questions. Often the animals have tumours produced by irradiation, viruses, chemicals or other *carcinogens*, or they may be genetically prone to develop cancer. The effect of dietary or other interventions on the prevention or progression of such tumours is then investigated.

A major strength of these studies is the tight control of experimental conditions. In addition, they are able to test interventions in a whole complex mammalian system (though caution is needed in extrapolating to humans), to explore the biological plausibility that a particular exposure can influence the cancer process or its occurrence. Results from animal studies provide evidence that may prompt more persuasive research; they can also corroborate findings from other types of study. There are also limitations to these types of studies: *dose-response* studies are often not conducted and those that are conducted are often short-term. Better models are required that mimic the carcinogenic cascade and include *metastatic spread* to other organs.

5.3 In vitro studies

Human or animal *cell lines* can sometimes be derived from human cancers and grown in vitro in the laboratory to help researchers understand mechanisms that may lead to the development of cancer.

Conducting studies in vitro has two main advantages. First, specific, well-defined interventions can be tested; second, biochemical and molecular mechanisms can be examined. Although cell culture can provide valuable data for specific *nutrients* or metabolites that are amenable to delivery to cells in vitro, it is difficult to mimic the complex interactions among the variety of nutrients and *bioactive constituents* found in food. Furthermore, many studies are compromised by doses of agents that far exceed physiologically relevant concentrations. These studies alone do not allow research of integrated systems, such as how organs or the whole body responds to the interventions, and thus direct extrapolation of results to humans is not warranted. Further development of relevant human laboratory models and application to critical questions about diet, nutrition and physical activity are necessary.

6. Methods of assessment

Some *exposures* are easier to measure than others. For example, it is relatively easy to assess the effect of tobacco smoking and exposure to tobacco on cancer risk. Although tobacco smoke is a mixture of many chemicals and its interactions with the body are complex, smoking can be considered a single exposure that is relatively easy for an individual to quantify. For example, people typically recall the ages of starting or stopping smoking, the types of cigarettes smoked and the number of packs per day or week.

By contrast, diets are multidimensional exposures and in free-living populations cannot be measured with accuracy. Moreover, the foods and drinks people consume every day contain thousands of constituents, some well-known, others unknown and unmeasured. The relationships between diet, nutrition, physical activity, and health and disease are complex and difficult to untangle. The presence or absence of *effect modification* (see **Box 1**) can create additional challenges.

6.1 Foods, drinks and nutrients

People's dietary intake varies from day to day and over the course of their lives. There are interrelationships between food components, between foods in whole diets and between diets and other behavioural characteristics such as physical activity or tobacco smoking. There are several methods for assessing food and drink consumption, all with their own weaknesses and strengths. See [Exposures: Wholegrains, vegetables and fruit](#); [Exposures: Meat, fish and dairy products](#); [Exposures: Alcoholic drinks](#); [Exposures: Non-alcoholic drinks](#) and [Exposures: Other dietary exposures](#) for issues in the interpretation of evidence for these *exposures*.

6.1.1 Dietary assessment methods

Dietary intakes can be measured for populations, groups or individual people. The most commonly used techniques for assessing food and drink consumption are food records or diaries, 24-hour dietary recalls, dietary histories and food frequency questionnaires (FFQs). A description of these methods and their advantages and disadvantages is available elsewhere [23]. Different approaches are appropriate for different types of questions; for instance, is the assessment of current or past diet, or is an accurate measurement of intake required rather than simply ranking people in order

of their intake? Most of the studies included in the CUP used dietary assessment data from people, recorded using FFQs. These questionnaires collect information on self-reported food consumption patterns, typically over the preceding year. A record is made of the frequency of consumption of 100 to 150 items and often includes information on serving sizes. FFQs may be designed to gain detailed information about specific aspects of diets, such as intakes of fats or *dietary fibre*, leaving other components less well characterised. A questionnaire for whole diets cannot adequately capture the full variety and composition of individual diets without becoming excessively burdensome for participants. However, FFQs are inexpensive and are practical for use in large-scale epidemiological studies. They can be self-administered in paper form, interviewer administered or completed using an online form. FFQs cannot give valid and reliable estimates of actual intake, including caloric intake, but they do robustly rank people in order of their intake. However, *adjustment* for energy intake is also undertaken in many studies.

All dietary assessment methods that rely on self-reporting are subject to measurement error (see **Box 1**). Further errors are introduced by the conversion of food data to *nutrient* data, using tables of the chemical composition of foods, which give average nutrient contents for defined foods [24]. Such tables do not take account of variations in food composition deriving from differing soil quality, harvesting conditions, animal feed, storage and food processing, for example. Furthermore, food tables can be incomplete: for instance, they may not include information on the *phytochemical* or *fatty acid* content of foods. In many countries, there may be no records of the composition of traditional and indigenous foods.

6.1.2 Biomarkers

Biological specimens such as urine, blood, toenails and hair can be used to replace estimates from dietary assessment methods or validate their accuracy [25]. *Biomarkers*, such as doubly labelled water used to estimate energy expenditure or 24-hour urinary nitrogen excretion used as a marker for protein intake, can be used to indicate the accuracy of various dietary assessment methods, but are not practical for use in large *cohort studies* due to their cost and burden on participants. Blood measures of some *fatty acids* or vitamins can be used to indirectly estimate dietary intake of these dietary constituents, as they tend to correlate with dietary intake. However, blood levels are determined not only by a person's intake of the compound, but also by factors such as the compound's bioavailability and excretion, the person's intakes of other dietary constituents, personal characteristics such as tobacco smoking and body fatness, and individual variation in metabolism. Consideration of time frame is important as some biomarkers are reflective of long-term *exposure* (for example, adipose tissue fatty acids), and some only short-term (for example, serum/plasma levels of vitamins). These determinants can vary among people, and this can *bias* observed diet-cancer associations [7]. For some dietary constituents, such as selenium and total sodium, biomarkers can provide a more accurate indicator of prevailing dietary intakes than data from FFQs [26].

For further information on the interpretation of evidence related to biomarkers in the CUP see [Exposures: Other dietary exposures](#).

6.2 Nutrition status

Nutrition status is not simply a function of dietary intake but is an integration of diet, body composition, and functional state and capacity, in the context of levels of physical activity. *Anthropometric measurements* are

important in the assessment of nutritional status, as they can be interpreted to indicate aspects of body composition, though they need to be interpreted carefully [27, 28]. These measures include BMI, waist circumference, *waist-hip ratio*, weight change, height and birthweight. For issues regarding interpretation of this evidence see [Exposures: Body fatness and weight gain](#); and [Exposures: Height and birthweight](#). Single anthropometric measurements do not capture changes during critical windows of susceptibility (that is, puberty and menopause), which presents a challenge in epidemiological research [28].

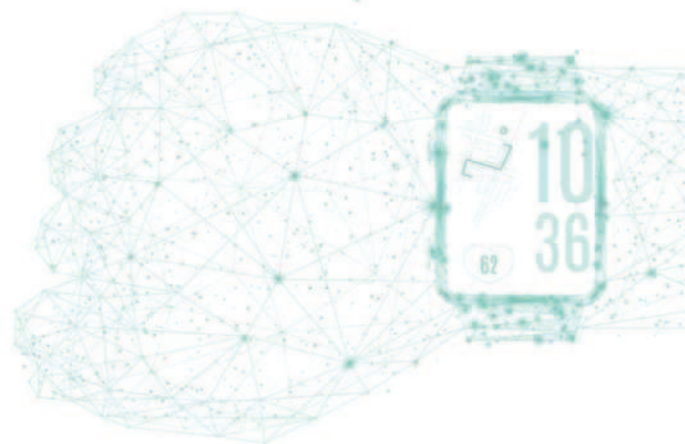
High BMI itself is not a cause of cancer. However, BMI and other measures of adiposity are judged to be the causal *exposures* for the development or progression of cancer in light of the extensive body of experimental evidence that supports the biological factors associated with adiposity and cancer. Equally, it is uncertain whether waist circumference or waist-hip ratio should be interpreted as markers of visceral adipose tissue specifically, of abdominal subcutaneous adipose tissue, or simply of total body fat [28].

Height acts as a marker for the complex interplay of genetic, nutritional and other environmental factors that determine the growth trajectory and culminate in final height [28].

Other measures of nutrition status are more difficult to measure but include assessment of dietary intake (see **Section 6.1.1**), *biomarkers of micronutrients* (see **Section 6.1.2**), and clinical measures such as handgrip strength.

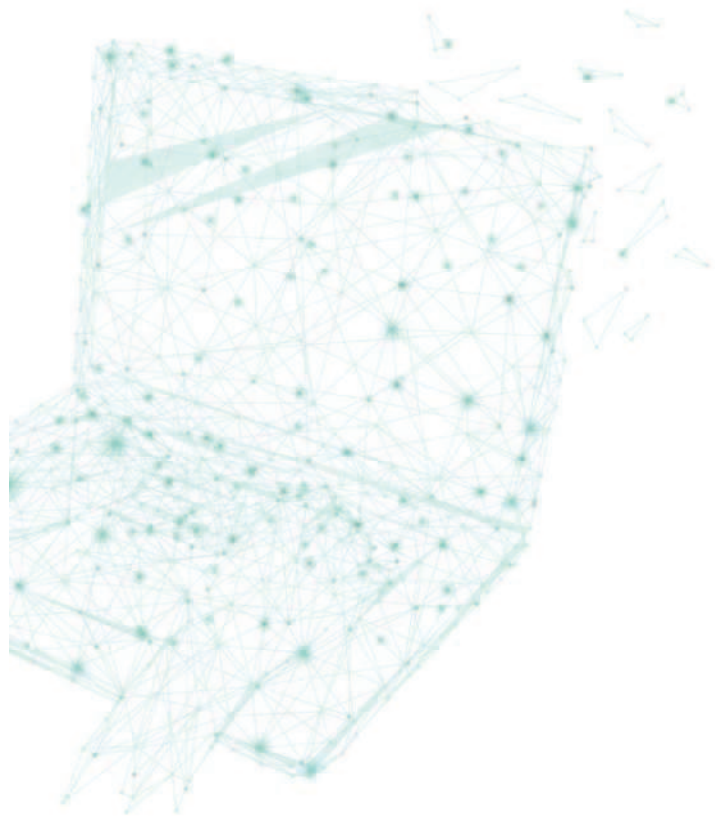
6.3 Physical activity

Research on the associations or effects of physical activity and health requires reliable and valid measurements of the type of physical activity (for example, aerobic or resistance training), as well as the frequency, duration and



intensity of physical activity and the context in which it occurs (recreational, occupational, household or transport). The effects of physical activity are not just a function of total overall energy expenditure – a person may expend the same amount of energy during a short period of intense exercise or a longer period of moderate activity, but the physiological effects may be different. It is also important to consider time spent in sedentary behaviours. Methods of assessment can be divided into objective (for example, instruments or monitors) or subjective (for example, interviewer or self-completed questionnaires) [29]. Epidemiological studies usually rely on self-completed questionnaires that vary in how they record the duration and type of physical activity, in the length and detail of the questionnaire, and in how the physical activity measures are calculated. Some may provide an estimate of the duration of physical activity (such as minutes per day), whereas others may simply categorise subjects (for example, as inactive, moderately active or active), according to specified cut-offs. A description of these methods and their advantages and disadvantages is available elsewhere [29]. Also see [Exposures: Physical activity](#) for information on types of physical activity included in the CUP and issues in the interpretation of evidence related to physical activity. Many questionnaires ask only about occupational activity or recreational activity and do not provide a comprehensive account of total physical activity.

6.4 Cancer outcomes



Some types of physical activity (such as recreational) are more likely to be reported reliably than others (such as household) simply because they represent a discrete activity over a defined time period. This may lend a misleading appearance of strength to associations with such measures.

More research is looking into the association of sedentary behaviours and risk of cancer. Sedentary behaviours involve both a high level of inactivity and a low level of activity. Issues related to capturing time spent doing sedentary activities, such as television viewing, video game playing, computer use, reading, talking on the telephone and sitting while commuting, include assessing the frequency and durations of these behaviours. These may be more difficult to assess than discrete physical activities such as swimming or walking to work. Some sedentary behaviours, such as television watching, may have other behaviours associated with them, such as snacking.

In studies of diet, nutrition, physical activity and cancer, accurately identifying cancer occurrence is as important as making accurate measures of diet, body fatness and physical activity. In most epidemiological studies, new cancers are identified through cancer registries, or else participants report whether they have been diagnosed as having cancer, and attempts are made to obtain confirmation from medical records or cancer registries. Many studies now report on sub-types of cancer, including molecular sub-types, and over time it is expected that more sub-types will be identified and recorded in patient reports and cancer registries. Studies may also require participants to undergo clinical examination or provide tissue biopsy samples to ensure sub-types are documented.

As cancer may take many years to develop, a sufficient length of follow-up (for example, 10 years or more) is required to determine the associations with cancer of the *exposures* (such as diet) measured at baseline. However, if the dietary and other habits of the population have been consistent over many years a shorter follow-up period will suffice. A longer follow-up time will also allow more cases of cancers to become evident and thus improve the ability to detect associations where they exist.

Screening programmes often detect smaller, more indolent tumours that have no symptoms. There are screening programmes for breast, colorectal and prostate cancers, but their availability varies around the world. Screen-detected cancer may differ from cancers diagnosed when symptoms arise, they may not be aggressive sub-types and they may not have the same risk factors.

7. Evidence collated for the Continuous Update Project

The CUP *systematic literature reviews* (SLRs) on specific cancers are updates of those completed for the 2007 Second Expert Report. These have all been conducted according to a common, detailed specification [30]. Some modifications were made to the methodology following the 2007 Second Expert Report – the updated literature searches were restricted to Medline and included only randomised controlled trials, cohort and nested case case-control studies.

The SLRs on cancer, breast cancer survivors, and energy balance and body fatness (a review of published reviews on the determinants of weight) form the main evidence for the assessments and judgements made by the Panel in the [Exposures sections](#), in [Energy balance and body fatness](#) and in the [CUP cancer reports](#). This is the evidence upon which the Panel bases its Recommendations (see [Recommendations and public health and policy implications](#)).

Also included in the Third Expert Report are assessments of the possible biological mechanisms that may underpin the causal associations.

Current practice, when resources allow, is to separate the process of collecting and displaying evidence from that of discussing and judging evidence. An important aspect of an SLR is that all stages of searching, selection, assessment and analysis are pre-specified, objective, reproducible, openly documented and subject to *peer review* at critical stages.

The work from the 2007 Second Expert Report [2] was used as a starting point. The first stage of the SLRs was a comprehensive search using a standardised search strategy for the scientific literature for *randomised controlled trials* and *cohort studies* published

since 2006 using Medline. Because *case-control studies* are particularly prone to recall (and other) *bias*, they were not routinely reviewed. However, if there were no or very few RCTs or cohort studies, they were included. Where necessary, the first option for case-control studies was to search for analyses from consortia of case-control studies, followed by published meta-analyses and then conducting CUP analyses of individual studies. Some examples include the inclusion of pooled analyses of case-control studies [31] for coffee and mouth, pharyngeal and laryngeal cancer (see [CUP mouth, pharynx and larynx cancer SLR 2016](#)), and conducting a CUP analysis for preserved vegetables and nasopharyngeal cancer (see [CUP nasopharyngeal cancer SLR 2017](#)). *Ecological studies* were also not routinely included; however, if limited information was available from other study designs and the Panel judged it important, reviews of ecological data from the 2007 Second Expert Report or other sources were included. An example is kidney cancer and arsenic in drinking water (see [CUP kidney cancer report 2015](#)).

Once the searches were completed, all papers identified were assessed for relevance using reproducible criteria. Study characteristics and results, informed by the framework developed by Bradford Hill [1], were extracted and recorded. Data from different studies, including those identified as part of the 2007 Second Expert Report, were combined and presented in plots comparing risk estimates of highest versus lowest levels of the *exposure* and analysed, using meta-analysis when appropriate. Full details of the approach taken can be found in the [CUP SLR protocols](#) and the [CUP SLRs](#).

Where possible the evidence was presented for the Panel in a number of ways. The plots comparing cancer risk between the highest versus lowest levels of exposure were used to provide some

information on direction of risk. A summary estimate is not usually presented in CUP cancer reports for these analyses unless dose-response meta-analyses are not possible. This is because the highest and lowest exposure categories are not the same in each study and hence the summary estimate could be misleading.

The Panel placed most weight on the dose-response meta-analyses. However, it did consider associations other than linear, using the non-linear dose-response analyses as these provide information on thresholds or plateaus (see **Box 2**). Sub-group analyses are also important to determine if the association differs by sex, smoking status, geographical location or cancer sub-type. Whether *bias* and confounding could be ruled out was also taken into account. All these points were considered by the Panel when interpreting the evidence.

Evidence from epidemiological studies and RCTs indicating a causal association between an aspect of diet and cancer is strengthened when there is evidence of a plausible biological pathway or mechanism by which the cancer process may be modified. The Panel agreed that the case for a causal relationship must include evidence of biological plausibility. Summaries of plausible biological mechanisms supporting the epidemiological evidence are presented in the exposure sections. The evidence on mechanisms has been based on both human and animal studies. Though not a systematic or exhaustive search, the expert reviews represent the range of currently prevailing hypotheses. Work to develop a more systematic process for reviewing the evidence from experimental studies for the CUP is continuing [32].

8. The grading criteria

The criteria have been developed as a means of operationalising within the context of diet, nutrition, physical activity and cancer the factors identified by Bradford Hill [1] as contributing to an inference of causation from observational data. They were developed by an independent expert Methodology Task Force and reviewed and revised by the Expert Panel for the 2007 Second Expert Report [2].

The purpose of the criteria is to provide a standardised framework within which the Panel can objectively categorise the likelihood that a dietary, nutritional or physical activity exposure is causally related to risk of cancer. The purpose of identifying causal links and distinguishing them from associations that are not judged to be causal is to support the Panel in making recommendations. Changing an exposure that is a causal factor can be expected to alter the outcome (that is, the risk of one or more cancers). As cancer is an important and increasing problem, and diet, nutrition and physical activity are recognised factors in its causation and progression, it is important to try to identify the links between them as a basis for clinical and public health policy.

The criteria lead to five possible levels of conclusion: convincingly causal; probably causal; limited evidence but suggestive of a possible causal relationship; limited evidence and no conclusion of a causal relationship possible; and substantial effect on risk unlikely (effectively a 'no effect' conclusion, though it is never possible to completely exclude an effect). However, the important distinction is between evidence that is judged strong enough to make a recommendation and evidence that is not strong enough to make a recommendation. The criteria state that conclusions of convincing or probable are strong enough

to support a recommendation, while evidence judged to fall into either of the limited categories is generally not strong enough to support recommendations. Importantly the criteria are not completely rigid but allow for flexibility through specified upgrading or downgrading factors – characteristics of the evidence that tend to strengthen or weaken confidence in an association being causal, such as a particularly large effect size or robust human experimental evidence. The Panel has sometimes not made recommendations despite strong evidence; this might be because of potentially adverse effects on one cancer despite evidence of protection for another (for example, calcium and/or dairy with prostate and colorectal cancer); or because it is not possible to craft a recommendation that is

useful in practice (as is the case for adult attained height). (For further information see [Recommendations and public health and policy implications](#).) Conversely, the Panel may make a recommendation for an exposure when there is a large volume of consistent, suggestive evidence for subgroups, as with non-starchy vegetables and fruit (as a group) and aerodigestive and some other cancers where as a whole the evidence was judged as probable decreases risk (see [Recommendations and public health and policy implications](#)). The Panel also considered the implications for other diseases when making recommendations, and so the recommendations can be considered to reduce the risk of other *non-communicable diseases* related to diet and physical activity.

Box 6: Criteria for grading evidence for cancer prevention

Adapted from Chapter 3 of the [2007 Second Expert Report](#) [2]. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are ‘convincing’, ‘probable’, ‘limited – suggestive’, ‘limited – no conclusion’, and ‘substantial effect on risk unlikely’. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see [CUP Breast cancer survivors report 2014](#)).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent *cohort studies*.
- No substantial unexplained *heterogeneity* within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including *confounding*, measurement error and *selection bias*.
- Presence of a plausible biological gradient (*‘dose–response’*) in the association. Such a gradient need not be linear or even in the same direction across the different levels of *exposure*, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five *case-control studies*.
- No substantial unexplained *heterogeneity* between or within study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and *selection bias*.
- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited – no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of *adjustment* for known *confounders*) or by any combination of these factors.

When an exposure is graded 'limited – no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (dietandcancerreport.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose-response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate *statistical power*. Defects such as these and in other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or humans that a specific mechanism exists or that typical exposures can lead to cancer outcomes argues against such a judgement.

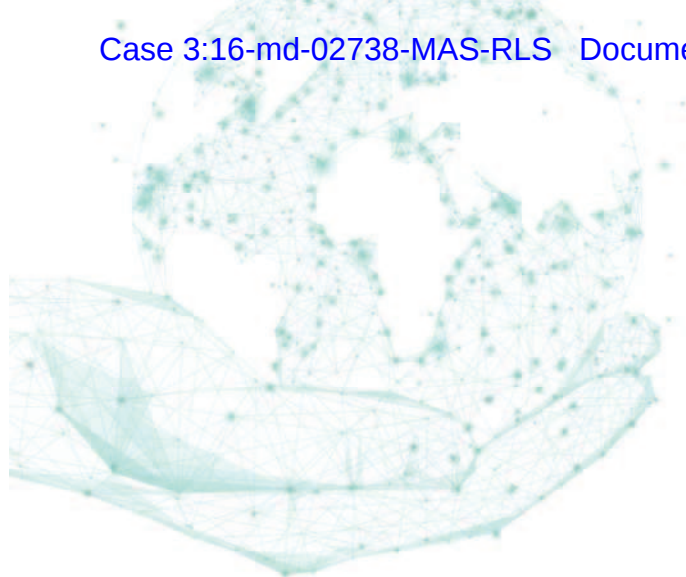
Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful and could overlap with judgements of 'limited – suggestive' or 'limited – no conclusion'.

SPECIAL UPGRADING FACTORS

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

Factors may include the following:

- Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.



8.1 Context for using the criteria

The ultimate aim of the criteria is to provide a standardised basis for the Panel's recommendations. The need for such criteria rests on two issues: first, the relevance of particular study designs to illuminate the questions of importance, and second, the impact on cancer risk of *exposures* that are complex, that are difficult to manipulate and that have their effect over decades or whole life spans, or even across generations. This is analogous to the situation described by Bradford Hill when addressing occupational exposures that would not be susceptible to testing through the most robust form of evidence, RCTs. When faced with a problem of public health significance, but without the possibility to test the causality of observed associations by RCTs, Bradford Hill noted that a best judgement needed to be made in order to allow consideration of public health interventions.

Bradford Hill was aware not only of the power of RCTs to vigorously test the effects of interventions or the causality of associations, but also of limitations in their application in certain contexts. Although the results of well-conducted and well-executed RCTs provide robust answers to certain questions, not all hypotheses can be tested. Many questions of

clinical importance can be directly tested, but controlled manipulation of diet and physical activity over a lifetime is clearly not readily amenable to such testing. RCTs have good internal validity (they give a robust answer to the question tested) but may have poor external validity (the question able to be tested is not directly applicable to the real-life situation). This may be for a range of reasons, for instance because of the use of atypical populations (such as those selected for high risk), or abnormal exposures (such as high-dose supplements), or simply because over the long term of an extended RCT differential attrition and *compliance* between the test and control groups mitigates the ability to ascribe differences in outcome to the test intervention. Although RCTs still inform overall judgements, the directness of the relationship of their results to the question of relevance may vary.

In contrast, prospective observational studies offer an opportunity to identify characteristics in real populations that are associated with real outcomes over long periods of time, although few *cohort studies* have lifetime exposure information. There is though the potential for confounding, which means that ascribing causality may be problematic. In practice, when faced with an important public health issue such as the impact of diet, a healthy weight and physical activity on cancer, where public guidance is needed, that guidance needs to be based on the best evidence, and this comes from a variety of sources, including observational data, RCTs and experimental evidence in laboratory models. The criteria offer a framework within which the process of assessing the evidence, drawing conclusions and making recommendations can take place.

Inevitably, it is problematic to attempt to isolate the impact of individual components of complex patterns of exposure, within which many components are associated with each other (for example, because they occur in the same foods). Therefore, there

is an even greater degree of certainty that the truly causal factor or factors lie within the identified broad pattern of exposure (that is, all the conclusions together), than there is for each singular component.

Although RCTs are now regarded as the norm for supporting clinical interventions, it is important to recognise that even in this setting, extrapolations from the evidence are usual in the case of individual patients (even if this is not always explicitly recognised by practitioners). For instance, the rigorous selection criteria in high-quality RCTs means that typical patients, who often have more than one condition, may not be eligible to participate. This rightly does not stop the practitioner applying professional judgement in the particular case, in the face of a degree of uncertainty about the evidence. Therefore, both clinical and public health practice rely on the recognition of the need for an intervention or guidance (for example, because of symptoms in patients or because of a preventable public health problem) and the application of professional judgement to the particular case in the face of incomplete evidence. Proof is a mathematical construct, and certainty is rarely attainable in biology. Therefore, when dealing with degrees of uncertainty it is important to be methodical about specifying the level of confidence expected to support an intervention or recommendations. That is what these criteria do.

8.2 Food-based approach

Terms used in the text of the Third Expert Report reflect the Panel's decision that its judgements and recommendations should, whenever possible, be based on foods and drinks rather than on *nutrients* or other *bioactive constituents*. This is in part because dietary constituents associated with foods are grouped with these foods. Thus, matrix entries in [Exposures: Wholegrains, vegetables](#)

and fruit list 'foods containing *dietary fibre*' (rather than dietary fibre), and in [Exposures: Alcoholic drinks](#) list 'alcoholic drinks' (rather than alcohol or alcohol as ethanol).

The food-based approach is also justified because of the uncertainty that any food constituent is a true causal factor, rather than simply a marker for the particular foods in which it is found or for other dietary constituents found in the same foods, or for other associated health-related factors. In [Exposures: Other dietary exposures](#), some supplements of *micronutrients* appear in matrices graded as 'convincing' or 'probable'. These judgements are derived from the findings of good-quality RCTs, sometimes also supported by observational studies, clearly showing that supplements of these micronutrients – rather than the foods containing them – affect the risk of cancer; as, for example, with beta-carotene supplements and lung cancer.

Sometimes the studies that are the basis for the Panel's work have used markers of *exposure*. Many epidemiological studies use BMI, waist circumference and *waist-hip ratio* as markers of body fatness. When there is clear evidence of an underlying mechanism for body fatness, the Panel has agreed that the term 'body fatness' best represents the causal factor (see [Exposures: Body fatness and weight gain](#)).

As exceptions to this approach, the Panel has made judgements on 'adult attained height' and 'greater birthweight', as shown in the matrices. Many epidemiological studies have reported on height and birthweight. It is thought that associations between height and cancer risk reflect some causal association with a combination of genetic, environmental, hormonal and nutritional growth factors affecting growth during the period from preconception to completion of linear growth. Uncertainty as to the precise mechanisms

underlying the observations with ‘adult attained height’ and ‘birthweight’ mean that the Panel was not able to determine the appropriate causal factors to be shown in the matrices (see [Exposures: Height and birthweight](#)). Instead, the *anthropometric markers* have been included, with appropriate footnotes.

8.3 CUP matrices

The matrices display the Panel’s judgements on whether particular aspects of diet, nutrition and physical activity do or may modify (or not modify) the risk of cancers of specific sites. Necessary clarifications and qualifications

are stated in footnotes to the matrices. In some cases, analysis may show that any association or effect begins or ends, or is less apparent, below or above evident ‘thresholds’ (see **Box 4**). For example, alcoholic drinks appear to increase the risk of some cancers (such as liver and colorectal) only above certain levels of consumption. Such amounts are specified in a footnote to the relevant matrices. When matrices include no such footnotes (as for alcohol and postmenopausal breast cancer), this is because no lower or upper threshold for the association or effect has been identified. In such cases, matrix entries showing or suggesting a causal association should be

Figure 1: Example of a summary matrix: physical activity and the risk of cancer

2018		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing	Physical activity ¹	Colorectum (colon) 2017 ²		
	Probable	Physical activity ¹	Breast (postmenopause) 2017 ³ Endometrium 2013 ⁵		
		Vigorous intensity physical activity	Breast (premenopause) 2017 ³ Breast (postmenopause) 2017 ³		
LIMITED EVIDENCE	Limited - suggestive	Physical activity ¹	Oesophagus 2016 ⁴ Lung 2017 Liver 2015 Breast (premenopause) 2017 ³	Sedentary behaviours	Endometrium 2013 ⁵
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

- 1 The exposure of physical activity includes evidence for all types of activity and all intensity levels.
- 2 The evidence for physical activity and colorectum is for colon cancer only – no conclusion was drawn for rectal cancer.
- 3 In addition to physical activity, there was sufficient evidence for the Panel to make a separate judgement for vigorous intensity physical activity and breast cancer (pre and postmenopause).
- 4 The evidence for physical activity and oesophageal cancer includes unspecified, adenocarcinoma and squamous cell carcinoma.
- 5 The evidence for sedentary behaviours and endometrial cancer was marked by sitting time.

taken to mean that the association or effect is across the whole range of dietary intake, amounts of physical activity or degrees of body fatness found in the studies analysed.

8.4 Levels and types of judgement

In **Figure 1** the top half of the matrix (labelled strong evidence) shows judgements for which the evidence for an association between an *exposure* and either decreased or increased cancer risk is convincingly or probably causal. A judgement of 'convincing' or 'probable' generally justifies a recommendation designed to inform policies and programmes designed to prevent cancer.

The top two rows of the matrix are separated from the row below, which shows judgements that the evidence is too limited, for a variety of reasons (see **Box 6**), to conclude that a relationship is causal, but that there are enough data to suggest that such a relationship might exist. Normally, a judgement of 'limited – suggestive' does not justify any recommendation. The matrices used in [CUP cancer reports](#) also include a row showing judgements where the evidence is so limited (again, for a variety of reasons) that no judgement can be made whether any association exists or not. For this reason, such judgements of 'limited – no conclusion' do not indicate whether the evidence is in the direction of decreasing or increasing risk. The final, bottom row of the matrix, 'substantial effect on risk unlikely', shows judgements for which the evidence shows that no causal relationship is likely to exist.

9. Conclusions

Reports such as this address issues of public importance. They are informed by a process of collection, display, discussion and judgement of evidence as the basis for recommendations made in the public interest.

We, the members of the Panel responsible for the Third Expert Report, have had the responsibility to ensure that the judgements and recommendations are clearly and reliably based on current scientific evidence.

We have built on the work of the previous 2007 Second Expert Report and have been supported by the evidence gathered and presented by Imperial College London and by the CUP's Secretariat.

No method used to ascertain causal relationships between diet, nutrition, physical activity and cancer is perfect. But we believe that the integrated and systematic approaches we have taken, summarised here, have enabled us to make sound judgements and reliable recommendations. We have also done our best to make sure that the methods we have used are explained and displayed transparently, so they can be readily accessed and challenged as science develops.

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Abbreviations

AICR American Institute for Cancer Research

BMI Body mass index

CI Confidence interval

CUP Continuous Update Project

FFQ Food frequency questionnaire

RCT Randomised controlled trial

RR Relative risk

SLR Systematic literature review

WCRF World Cancer Research Fund

Glossary

Adenocarcinoma

Cancer of glandular epithelial cells.

Adjustment

A statistical tool for taking into account the effect of known confounders (see **confounder**).

Anthropometric measures

Measures of body dimensions.

Bias

In epidemiology, consistent deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to the study type or analysis (see **selection bias**).

Bioactive constituents

Compounds that have an effect on a living organism, tissue or cell. In nutrition, bioactive compounds are distinguished from nutrients.

Biomarker

A naturally occurring molecule, gene or characteristic by which a particular pathological or physiological process can be identified.

Body mass index (BMI)

Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m²). Provides an indirect measure of body fatness.

Carcinogen

Any substance or agent capable of causing cancer.

Carcinogenesis

The process by which a malignant tumour is formed.

Case-control study

An epidemiological study in which the participants are chosen on the basis of their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as tobacco smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cell line

A cell culture developed from a single cell and therefore consisting of cells with a uniform genetic make-up.

Cohort study

A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later) and followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, tobacco smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

Compliance

The extent to which people such as study participants follow an allocated treatment programme.

Confidence interval (CI)

A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the association of tobacco smoking and relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95% chance that the true value lies between 5 and 15.

Confounder

A variable that is associated with both an exposure and a disease but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that tobacco smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (adjusted) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

Diet, nutrition and physical activity

In the CUP, these three exposures are taken to mean the following: **diet**, the food and drink people habitually consume, including dietary patterns and individual constituent nutrients as well as other constituents, which may or may not have physiological bioactivity in humans; **nutrition**, the process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair, often marked by nutritional biomarkers and body composition (encompassing body fatness); and **physical activity**, any body movement produced by skeletal muscles that requires energy expenditure.

Dietary fibre

Constituents of plant cell walls that are not digested in the small intestine. Several methods of analysis are used, which identify different components. The many constituents that are variously included in the definitions have different chemical and physiological features that are not easily defined under a single term. The different analytical methods do not generally characterise the physiological impact of foods or diets. Non-starch polysaccharides are a consistent feature and are fermented by colonic bacteria to produce energy and short chain fatty acids including butyrate. The term ‘dietary fibre’ is increasingly seen as a concept describing a particular aspect of some dietary patterns.

Dose–response

A term derived from pharmacology that describes the degree to which an association or effect changes as the level of an exposure changes, for instance, intake of a drug or food.

Ecological study

A study in which differences in patterns of exposure, for instance in consumption of a particular nutrient or food, are compared at aggregate level, with populations (rather than individual people) as the unit of analysis.

Effect modification

Effect modification (or effect-measure modification) occurs when the effect of an exposure differs according to levels of another variable (the modifier).

Exposure

A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

Fatty acid

A carboxylic acid with a carbon chain of varying length, which may be saturated (no double bonds) or unsaturated (one or more double bonds). Three fatty acids attached to a glycerol backbone make up a triglyceride, the usual form of fat in food and adipose tissue.

Heterogeneity

A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the I² test.

High-income countries

As defined by the World Bank, countries with an average annual gross national income per capita of US\$12,236 or more in 2016. This term is more precise than and used in preference to 'economically developed countries'.

Low-income countries

As defined by the World Bank, countries with an average annual gross national income per capita of US\$1,005 or less in 2016. This term is more precise than and used in preference to 'economically developing countries'.

Meta-analysis

The process of using statistical methods to combine the results of different studies.

Metastatic spread

The spread of malignant cancer cells to distant locations around the body from the original site.

Micronutrient

Vitamins and minerals present in foods and required in the diet for normal body function in small quantities conventionally of less than 1 gram per day.

Nested case-control study

A case-control study in which cases and controls are drawn from the population of a cohort study; often used for studies of prospectively collected information or biological samples.

Non-communicable diseases (NCDs)

Diseases which are not transmissible from person to person. The most common NCDs are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes.

Nutrient

A substance present in food and required by the body for maintenance of normal structure and function, and for growth and development.

Peer review

The scrutiny of scientific papers by one or more suitably qualified scientists.

Phytochemicals

Non-nutritive bioactive plant substances that may have biological activity in humans.

Point estimate

An estimate that is reported as a single value. The precision of a point estimate is indicated by the width of the confidence interval that surrounds it.

Pooled analysis

In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Processed meat

Meats transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation (see [Exposures: Meat, fish and dairy products](#)).

Randomised controlled trial (RCT)

A study in which a comparison is made between one intervention (often a treatment or prevention strategy) and another (control). Sometimes the control group receives an inactive agent (a placebo). Groups are randomised to one intervention or the other, so that any difference in outcome between the two groups can be ascribed with confidence to the intervention. Sometimes, neither investigators nor subjects know to which intervention they have been randomised; this is called 'double-blinding'.

Relative risk (RR)

The ratio of the rate of an outcome (for example, disease (incidence) or death (mortality)) among people exposed to a factor, to the rate among the unexposed, usually used in cohort studies.

Selection bias

Bias arising from the procedures used to select study participants and from factors influencing participation.

Socioeconomic status

A combined product of social and economic status reflecting education level, personal wealth, class and associated factors.

Statistical power

The power of any test of statistical significance, defined as the probability that it will reject a false null hypothesis.

Systematic literature review (SLR)

A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

Waist–hip ratio (WHR)

A measure of body shape indicating central (abdominal) fat distribution.

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Our Cancer Prevention Recommendations

Be a healthy weight

Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active

Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans

Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of ‘fast foods’ and other processed foods high in fat, starches or sugars

Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat

Eat no more than moderate amounts of red meat, such as beef, pork and lamb.
Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks

Drink mostly water and unsweetened drinks

Limit alcohol consumption

For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention

Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can

Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can

Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

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